REMARKS

In the Office Action dated December 4, 2003, claims 1-7, 22-25, 32-35 and 42-99 are pending. Claims 2, 22-25, 33-34, 44, 52-74, 76, 80, 88, 92, 97 and 99 are withdrawn from further consideration as drawn to non-elected subject matter. Claim 43 is objected to for certain alleged informalities. Claims 3-5, 7, 35, 42-43, 45-51, 96 and 98 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1, 4-5, 32, 87, 89-91, and 94-95 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Reff (U.S. Patent No. 5,648,267). Claims 1, 4-5, 32, 75, 77-79, 87, 89-91 and 94-95 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Reff in view of Haselkorn et al. (U.S. Patent No. 6,306,636 B1). Claims 1, 4-5, 32, 75, 77-79, 82-87, 89-91, and 94-95 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Reff and Haselkorn et al. as applied to claims 1, 4-5, 32, 75, 77-79, 87, 89-91 and 94-95 above, and further in view of Engler et al. (U.S. Patent No. 5,262,316) and Hansen et al. (U.S. Patent No. 6,051,409). The declaration is also objected to as allegedly defective.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The Examiner objects to the declaration as defective, because the alteration to the address of the co-inventor, Xue-Qing Wang, was not initialed. Applicants provide herewith a substitute declaration signed by Xue-Qing Wang. Withdrawal of the objection to the declaration is therefore respectfully requested.

Claim 43 is objected to because the claim does not end in a period.

Applicants have amended claim 43 to add a period. Withdrawal of the objection to claim 43 is therefore respectfully requested.

Claims 3-5, 7, 35, 42-43, 45-51, 96 and 98 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Regarding Claims 42, 96 and 98, the Examiner alleges that the use of "[$y_1y_2y_3$]" lacks antecedent basis. Applicants believe that the Examiner is referring to the y^{II}-series presented in square brackets at the end of these claims, as the y^{II}-series is presented in curled brackets in the general formula at the beginning of these claims. Applicants have amended claims 42, 96 and 98 to uniformly refer to the y^{II}-series in curled brackets.

Furthermore, the Examiner alleges that claims 42, 96 and 98 do not expressly recite how the nucleotide triplets in the recited sequences are altered to generate the ATG triplets. Applicants respectfully submit that one skilled in the art would be well aware of the myriad of ways in which a nucleotide sequence may be altered to generate a specific sequence. Applicants respectfully direct the Examiner's attention to page 26 of the specification, where exemplary methods for alteration of a nucleotide sequence are described.

The Examiner also contends that the recitation "comprising altering the nucleotide triplets...to introduce...an RTG or RUG" in claims 42, 96 and 98 is indefinite. The Examiner indicates that the general formula in claim 42 already comprises three RTG triplets, and therefore it is unclear as to whether modification of the sequence refers to the insertion of additional ATG triplets.

Applicants respectfully submit that the structural formula in Claim 42 *may* contain up to three ATG triplets, or alternatively may contain as few as no RTG triplets. This is dependent on the values of n, p and r in the general formula and whether $x_1x_2x_3$ encodes an RTG codon or a

different codon, as clearly defined in the general formula. Furthermore, Applicants respectfully submit that the present methods are achieved by adding ATG triplets to any given 5' UTR to reduce the expression of a protein-coding sequence coupled to the 5' UTR. Furthermore, Applicants respectfully submit that the effect of adding ATG triplets is both relative and additive. For example, addition of an ATG triplet to the 5' UTR of a protein-encoding sequence would relatively reduce the expression of the protein-encoding sequence whether the 5' UTR has 0, 1, 2, or 3 pre-existing RTG triplets. Furthermore, Applicants respectfully submit that the structure in Claim 42 merely defines a starting sequence to which ATG triplets may be added, and whether this structure does or does not comprise pre-existing ATG (or RTG) triplets, does not materially affect the results of the claimed methods, i.e., of reducing the expression of the sequence coupled to the 5' UTR.

The Examiner further alleges that the term "derived from the GLI1 gene leader sequence" recited in claim 46 is indefinite. The Examiner contends that the metes and bounds of what constitutes a derivative of a GLI1 gene leader sequence are unclear. Applicants have amended claim 46 by deleting the term "derived". Claim 46, as amended, recites that the nucleotide sequence is a GLI1 gene leader sequence or fragment thereof. It is respectfully submitted that claim 46 as amended is not indefinite.

Regarding claims 47, the Examiner considers the recitation "low stringency conditions" as indefinite. It is observed that the same language also appears in claims 48-51. Applicants have amended claims 47-51 to recite stringency conditions of 2x SSC buffer, 0.1%w/v SDS at 42°C. Support for this amendment is found in the specification at page 39, lines 5-23.

Claims 1, 4-5, 32, 87, 89-91, and 94-95 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Reff (U.S. Patent No. 5,648,267).

It is observed that the present claims are directed to methods of modulating the expression of a genetic sequence by introducing or removing one or more RTG or RUG triplets in the 5' nucleotide sequence upstream of the authentic translation initiation site of the genetic sequence.

According to the Examiner, Reff teaches a translationally impaired selectable marker gene of an expression vector by adding an ATG triplet upstream of the authentic ATG start site of the selectable marker gene. Reff allegedly teaches that the added start codon is intended to impair the translation of the selectable marker gene. The Examiner also alleges that Reff teaches that the impairment of the translation of the selectable marker of an expression vector improves the expression efficiency of the heterologous gene, which is also present in the vector.

Applicants respectfully disagree with the Examiner. Reff teaches the translational impairment of a selectable marker gene by modification or impairment of the Kozak sequence of the selectable marker gene. It is apparent from Reff that impairment of the translation of the selectable marker gene requires a fully impaired Kozak sequence. See, col. 3, lines 25-28 and 47-50; col. 3, line 65 through line 8. Reff further discloses that an out-of-frame ATG codon upstream of the impaired Kozak sequence may further enhance the effect of the Kozak sequence impairment. However, Reff does not teach that the insertion of ATG codons in the 5' UTR of a gene alone, absent a fully impaired Kozak sequence, is sufficient to reduce the translation of a downstream gene. In fact, Reff does not teach that adding a start codon upstream of the authentic start site, absent the fully impaired Kozak sequence, would have any effect on the translation of the selectable marker gene. Therefore, Applicants respectfully submit that Reff

does not teach or suggest the addition of an ATG codon as an independent means for downregulating translation, as presently claimed.

In contrast, the present application discloses the specific effect of RTG codons (wherein R may be, *inter alia*, A) in the 5' UTR of a gene. The present application also discloses that the addition of RTG codons to the 5' UTR alone is sufficient to suppress translation of a downstream gene, while removal of RTG codons from a 5' UTF can up-regulate translation of a downstream gene. Accordingly, Applicants respectfully submit that the present invention identifies the specific contribution of RTG codons in the 5' UTR of a gene, independent of the presence of an impaired Kozak sequence as taught by Reff.

In view of the foregoing, it is respectfully submitted that the presently claimed methods are not taught or suggested by Reff. Withdrawal of the rejection under §102(b) based on Reff is therefore respectfully requested.

Claims 1, 4-5, 32, 75, 77-79, 87, 89-91 and 94-95 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Reff in view of Haselkorn et al. (U.S. Patent No. 6,306,636 B1).

The Examiner admits that Reff does not specifically teach translationally impairing a gene in plant cells. The Examiner contends that Haselkorn et al. teach that the upstream AUG codons, some of which are found in plants, are believed to affect the efficiency of mRNA translation and thus may be important in the regulation of expression of some genes. Therefore, the Examiner is of the opinion that it would have been obvious to one of ordinary skill in the art to modify the method taught by Reff by substituting the animal cells taught by Reff with plant cells. The Examiner contends that one would have been motivated to do so for the expected

benefit of increasing the expression of heterologous genes in plant cells as taught by the combination of the cited references.

As submitted above, Reff does not teach or suggest the addition of an ATG codon as an independent means for downregulating translation, as presently claimed. Applicants respectfully submit that the Haselkorn et al. reference does not cure the deficiency of Reff. Applicants observe that Haselkorn et al. only mention in mere passing that "the upstream AUGs are believed to affect the efficiency of mRNA translation and as such may be important in the regulation of expression of some genes." Applicants respectfully submit that this statement by Haselkorn et al. does not teach or suggest how ATG codons upstream of an 'authentic' start codon in mRNA actually would affect translation efficiency. Specifically, there is no teaching or suggestion in Haselkorn et al. as to whether the number of ATG codons in a 5' UTR of a given gene can be modified to increase or decrease translation of the downstream gene.

Accordingly, Applicants respectfully submit that the cited references, taken alone or in combination, do not teach the claimed invention. As such, withdrawal of the rejection of claims 1, 4-5, 32, 75, 77-79, 87, 89-91 and 94-95 based on Reff in view of Haselkorn et al. is respectfully requested.

Claims 1, 4-5, 32, 75, 77-79, 82-87, 89-91, and 94-95 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Reff and Haselkorn et al. as applied to claims 1, 4-5, 32, 75, 77-79, 87, 89-91 and 94-95 above, and further in view of Engler et al. (U.S. Patent No. 5,262,316) and Hansen et al. (U.S. Patent No. 6,051,409).

The Examiner admits that Reff and Haselkorn et al. do not specifically teach methods involving plant cells from cotton or a cereal crop, or involving a target sequence that confers

resistance to a herbicide or pesticide. The Examiner contends that these features are taught by Engler et al. and Hansen et al.

Applicants reassert that the Reff reference and the Haselkorn et al. reference in combination do not teach or suggest the addition of an ATG codon as an independent means for downregulating translation, as presently claimed. Applicants respectfully submit that the secondary references, Engler et al. and Hansen et al., do not cure the deficiency of Reff or Haselkorn et al. Therefore, the methods of claims 1, 4-5, 32, 75, 77-79, 82-87, 89-91 and 94-95, are unobvious in view of Reff and Haselkorn et al. and further in view of Engler et al. and Hansen et al. As such, withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, the present application is in condition for allowance which action is earnestly solicited.

Respectfully submitted,

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Enc.: Substitute Declaration